Original Article / Özgün Makale

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1138232

J Med Palliat Care 2022; 3(3): 165-168

Comparison of intrahepatic cholestasis incidence and maternal perinatal outcomes in fresh and frozen embryo transfers

Taze ve dondurulmuş embriyo transferlerinde intrahepatik kolestaz insidansı ve maternal perinatal sonuçların karşılaştırılması

Murat Önal[1], Mehmet Ağar[2], Tuğba Gürbüz[3]

[1]Gynolife IVF Clinic, Lefkosa, Cyprus
[2]Private Clinic, Şanlıurfa, Turkey
[3]Medistate Hospital Gynecology and Obstetric Clinic, İstanbul, Turkey

Cite this article as/Bu makaleye atıf için: Önal M, Ağar M, Gürbüz T. Comparison of intrahepatic cholestasis incidence and maternal perinatal outcomes in fresh and frozen embryo transfers. J Med Palliat Care 2022; 3(3): 165-168.

ABSTRACT

Objective: To compare the perinatal and maternal results of intrahepatic cholestasis (ICP) in fresh and frozen-thawed embryo transfer (ET) pregnancies.

Material and Method: This research was performed retrospectively, including fourty-five pregnant women applied to our hospital between October 2010 and January 2021. Two groups have been determined, group:1 (Frozen thawed; n:21) and group:2 (Fresh; n:24). Common pruritus in the body and high fasting bile acids (FBA) levels (greater than 10 mmol/L) were accepted as diagnostic criteria. The exclusion criteria were spontaneous pregnancies, multiple pregnancies, chronic liver disease history. SPSS, version 26 was used for statistical analysis.

Results: Statistically significant difference could not be associated between the two groups regarding age, maternal body mass index (BMI), smoking status, number of trials, gestational diabetes mellitus (GDM), types of infertility and polycystic ovary syndrome (PCOS) incidence (p-value >0.05). The way of birth, gender, congenital anomaly, need for meconium aspiration syndrome (MAS), weight of newborn at birth, neonatal intensive care unit (NICU), gestational age at birth and 5 min Apgar score also compared and significantly difference could not be associated between two groups (p-value > 0.05).

Conclusion: This study supports the fact that frozen-thawed and fresh in vitro fertilization (IVF) pregnancies in terms of maternal characteristics and perinatal results have no difference.

Keywords: Intrahepatic cholestasis of pregnancy, fresh embryo transfer, frozen-thawed embryo transfer, perinatal outcomes

ÖZ

Amaç: Taze ve dondurulmuş çözülmüş embriyo transferi (ET) gebeliklerinde intrahepatik kolestazın perinatal ve maternal sonuçlarını karşılaştırmak.

Gereç ve Yöntem: Bu araştırma, Ekim 2010-Ocak 2021 tarihleri arasında hastanemize başvuran 45 gebe kadın ile retrospektif olarak yapılmıştır. Grup:1 (Dondurulmuş çözülmüş; n:21) ve Grup:2 (Taze: n:24) olmak üzere iki grup belirlenmiştir. Vücutta yaygın kaşıntı ve yüksek açlık safra asitleri (FBA) seviyeleri (10 mmol/L'den fazla) tanı kriteri olarak kabul edildi. Dışlama kriterleri spontan gebelikler, çoğul gebelikler, kronik karaciğer hastalığı öyküsü idi. İstatistiksel analiz için SPSS, versiyon 26 kullanıldı.

Bulgular: Yaş, vücut kitle indeksi (VKİ), sigara içme durumu, deneme sayısı, gestasyonel diabetes mellitus (GDM), infertilite türleri ve polikistik over sendromu (PCOS) insidansı açısından iki grup arasında istatistiksel olarak anlamlı bir fark bulunmamıştır (p >0.05). Doğum şekli, cinsiyet, konjenital anomali, mekonyum aspirasyon sendromu (MAS), doğumdaki yenidoğan ağırlığı, yenidoğan yoğun bakım ünitesi (YYBB), doğumdaki gebelik yaşı ve 5 dk Apgar skoru da karşılaştırılmış ve anlamlı fark bulunamamıştır (p>0.05).

Sonuç: Bu çalışma, donmuş çözülmüş ve fresh tüp bebek gebeliklerinin maternal özellikler ve perinatal sonuçlar açısından farklılık göstermediğini desteklemektedir.

Anahtar Kelimeler: Gebeliğin intrahepatik kolestazı, taze embriyo transferi, donmuş çözülmüş embriyo transferi, perinatal sonuçlar

Corresponding Author/Sorumlu Yazar: Tuğba Gürbüz, Rüzgarlıbahçe Mah. Cumhuriyet Cad. No:34 Medistate Hospital Gynecology and Obstetric Clinic, İstanbul, Turkey
E-mail/E-posta: drtgurbuz@hotmail.com
Received/Geliş: 30.06.2022 **Accepted/Kabul:** 12.08.2022

This work is licensed under a Creative Commons Attribution 4.0 International License.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease in the pregnancy (1). During the pregnancy period, women experience several diseases and concerns (2-5). ICP is a disorder which is specifically seen in pregnancy, which has been reported to be prevalent by 0.3-5.6%. This disease is more common in advanced age pregnants, women using contraceptives, and multiparous women (6). Pruritus is one of the major symptoms of ICP. When the bile acid level is more than 10 mmol/L, pruritus will occur. This is observed in the second and third trimesters. Other symptoms such as jaundice, nausea, and appetite loss have been also reported in patients (7,8). At present, this disease has unknown causes but hormone, environmental and genetic factors interfere in the outbreak of this disease (9). The hormone factors are more important than other factors. Family history in mothers, sisters, or daughters of the patients is among the important warning factors. This disease is more prevalent in some special tribal groups (10). To prevent this disease, estrogen levels should be controlled. High estrogen level causes reduced biliary excretion and finally increase biliary acids, liver enzymes, and bilirubin. It is important to prevent high estrogen levels to prevent ICP (11). High estrogen levels are associated with women's liver, reducing biliary excretion and increasing biliary acids, elevated liver enzymes, and bilirubin levels (12). ICP is a benign illness for women, however it has severe perinatal consequences. Timely diagnosis of ICP is highly important for the neonate. Clinical investigations and timely diagnosis of the disease can prevent stillbirth or preterm labor. Therefore, early diagnosis is vital for curing this disease (9). ICP has no meaningful effects for the mother, but stillbirth, meconium-stained amniotic fluid, preterm labor, respiratory distress syndrome have been noted in pregnancies with ICP (13). The disease risks for the fetus are directly associated with biliary acids level. Increasing the biliary acids level threatens the fetus (14).

The frequency of ICP was compared between in vitro fertilization (IVF) and spontaneous pregnancies in many studies. But there is no study in the literature comparing increased ICP risk concerning embryo transfer way fresh or frozen-thawed. This study compares the laboratory, perinatal characteristics, and maternal of fresh and frozen-thawed embryo transfer pregnancies.

MATERIAL AND METHOD

The study was carried out with the permission of Doğu Akdeniz University Clinical Researches Ethics Committee (Date: 24.05.2022, Decision No: 2022-0148). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was performed retrospectively including forty-five pregnant women between October 2010 and January 2021 at a private hospital. The data was collected from the data processing system records. When the fasting bile acids (FBA) levels more than 10mmol/L and common pruritus in the body diagnose can be done. The exclusion criteria were spontaneous pregnancies, multiple pregnancies, chronic liver disease history. Also, women with comorbidity like hypothyroidism, chronic renal failure, chronic hypertension, hyperthyroidism, hematological or rheumatologic disease, and heart disease were excluded from the analysis. Two patient groups have been determined according to their embryo transfer method as fresh and frozen-thawed. The maternal data of the patients in fresh and frozen-thawed groups were analyzed. Maternal data included smoking status, body mass index (BMI: kg/m2), age, number of trials, polycystic ovary syndrome (PCOS) status, Gestational Diabetes Mellitus (GDM) and types of infertility of the patients (primer and secondary). Perinatal outcomes included way of birth, gender, congenital anomaly status, necessity for neonatal intensive care unit, birth weight, meconium aspiration syndrome (MAS), gestational age at birth, and the 5-min APGAR score. To calculate the sample size with the GPower program, the total mean of the two compared groups with the power of 70%, effect size of 80%, and 0.05 type 1 error was at least 42 patients (15).

Statistical Analysis

Data were analyzed, tabulated, and subjected to using the SPSS, version 26. A p-value of < 0.05 was accepted as statistically significant. The continuous data were displayed as mean±SD. At the same time, categorical data were illustrated as numbers and percentages. The Kolmogorov-Smirnov test of normality was utilized to test the normality hypothesis. Based on the test results, proper parametric (Independent t-test) and nonparametric tests (Mann Whitney and Chi-square test) were used.

RESULTS

The sample consisted of 45 women, including 21 women with frozen-thawed and 24 women with fresh method aged 22 to 43 years (33.22±4.08). **Table 1** shows maternal characteristics of study groups. We evaluated the patients' maternal characteristics; maternal age at transfer was 33.19±3.45 years in the frozen-thawed group and 33.26±4.66 years in the fresh group (p-value>.05). There was no statistically significant difference between the two groups regarding BMI (frozen-thawed: 24.66±1.85 vs. fresh: 24.87±1.62, p-value>0.05). There was not a statistically significant difference between frozen-thawed group and fresh in terms of smoking status (p-value >0.05), number of trials (frozen-thawed: 1.85±0.79 vs. fresh: 1.87±1.26, p-value>0.05), types of infertility (p-value=0.923), PCOS (p-value>0.05), and GDM (p-value>0.05).

Table 1. Maternal characteristics of study groups

Variable	Categories	Frozen-thawed (n=21) (Mean±SD) or n (%)	Fresh (n=24) (Mean±SD) or n (%)	P-value
Age(yr)		33.19±3.45	33.26±4.66	0.955*
BMI		24.66±1.85	24.87±1.62	0.692*
Smoking				0.482***
	Yes	19 (90)	20 (83)	
	No	2 (10)	4 (17)	
Number of trials		1.85±0.79	1.87±1.26	0.474**
Types				0.923**
	Primer	20 (95)	23 (96)	
	Secondary	1 (5)	1 (4)	
PCOS				0.153***
	No	16 (76)	22 (92)	
	Yes	5 (24)	2 (8)	
GDM				0.153***
	No	16 (76)	22 (92)	
	Yes	5 (24)	2 (8)	

* Independent-Samples t-test ** Mann–Whitney U test ***Pearson Chi-Square Test
"PCOS; polycystic ovary syndrome", "GDM; gestational diabetes mellitus"

Table 2 shows perinatal characteristics of study groups. Statistically significant difference could not be shown between frozen-thawed group and fresh in terms of way of birth (p-value>0.05), gender (p-value>0.05), congenital anomaly (p-value>0.05), need for neonatal intensive care unit (NICU) (p-value>0.05), and MAS (p-value >0 .05). There was no statistically significant difference between the two groups in terms of birth weight (frozen-thawed 3030.95±360 vs. fresh: 2928.57±311, p-value >0.05), gestational age at birth (frozen-thawed: 37.19±0.60 vs. fresh: 37.20±0.50, p-value >0.05) and 5 min APGAR score (frozen-thawed: 8.09±0.88 vs. fresh: 8.19±0.98, p-value >0 .05). When comparing the two groups in terms of perinatal results, no statistically significant difference was found between them.

Table 2. Perinatal results of study groups

Variable	Categories	Frozen-thawed (n=21) (Mean±SD) or n (%)	Fresh (n=24) (Mean±SD) or n (%)	P-value
Way of birth				0.751***
	C/S	19 (90)	21 (87)	
	Vaginal delivery	2 (10)	3 (13)	
Gender				0.688***
	Male	11 (52)	14 (58)	
	Female	10 (48)	10 (42)	
Congenital anomaly				0.889***
	No	19 (90)	22 (92)	
	Yes	2 (10)	2 (8)	
Need for NICU				0.751***
	No	19 (90)	21 (87)	
	Yes	2 (10)	3 (13)	
Mass				0.923***
	No	20 (95)	23 (96)	
	Yes	1 (5)	1 (4)	
Birth weight (gr)		3030.95±360	2928.57±311	0.331*
Gestational age at birth (weeks)		37.19±0.60	37.20±0.50	0.967**
5 min Apgar score		8.09±0.88	8.19±0.98	0.765**

* Independent-Samples t-test ** Mann–Whitney U test ***Pearson Chi-Square Test
"C/S: caeserian section" "NICU: neonatal intensive care unit"

DISCUSSION

A raised incidence of ICP and fetal danger during pregnancy behind IVF has been documented in several kinds of research (16). In this study, in which frozen and frozen-thawed IVF pregnancies were assessed, the demographic and perinatal characteristics of the two groups were compared by retrospective analysis of 45 pregnancies with ICP.

In this study, there were no differences between the frozen-thawed group and fresh group in terms of maternal characteristics. Although there is a difference in maternal characteristics between healthy pregnant women and with ICP, there is no difference in maternal characteristics between pregnant women with ICP by various fertilization methods (16-18).

Providing, maintaining, and promoting the health of infants as a vulnerable group has a remarkable place in health services. ICP is associated with increased perinatal risks such as a higher rate of newborn intensive care admissions, the 5-min APGAR score increases, birth weight, and stillbirth. In line with other studies' results, in this study, there were no differences in perinatal results, and there was no difference between the frozen-thawed group and fresh in terms of gestational age at birth, birth types, congenital anomaly, gender, NICU admission rate, birth weight, and the 5-min APGAR score. The effect of fertilization methods such as IVF and spontaneous on perinatal results has been studied in many research, and no significant difference has been observed between fertilization methods and perinatal results (16-18). However, in twin pregnancies, the IVF method increases risks of ICP perinatal results (19-21). Birth weight is one of the most critical health indicators for evaluating newborns and infant health indexes (22). According to research, the birth weight of pregnant women with ICP is lower than that of normal pregnancies (23). There was no significant relationship between birth weight in the fresh and frozen-thawed groups, but the average birth weight in the frozen-thawed method was about 100 grams higher than the fresh method. The gestational age at birth and 5-min APGAR scores in both groups were very close.

The entire study implementation process, including IVF, follow-up, and delivery, was performed in our hospital. In order to avoid bias in recalling and interviewing participants, all participants' data were collected from their electronic medical records in the hospital system. On the one hand, this nature of our study method provides accurate access to all patient details and, on the other hand, limits the number of small samples because the number of ICP occurrences in pregnancy is very low. Therefore, the small number of samples can be mentioned as the main limitation of this study.

CONCLUSION

This paper supports that there is no difference between frozen-thawed and fresh IVF pregnancies in maternal characteristics and perinatal results. Management of pregnant women with ICP is recommended regardless of fertilization methods. Twin pregnancies are more affected with ICP, and the impact of fertilization methods on twin pregnant women with ICP in future work should be given more attention..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Doğu Akdeniz University Clinical Researches Ethics Committee (Date: 24.05.2022, Decision No: 2022-0148).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

REFERENCES

1. Chappell LC, Bell JL, Smith A, et al. PITCHES study group. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. Lancet 2019; 394: 849-60.
2. Dokuzeylül Gungor N, Gurbuz T. Pregnancy outcomes of intrauterine insemination in age-matched young women according to serum anti-mullerian hormone levels. JRM, 2021; 66: 195-202.
3. Gürbüz T,Gökmen O,Dokuzeylül Gungor N, Polikistik over sendromu bulunan kadınlarda glikoz potasyum oranının tanısal değerinin insülin ile karşılaştırılması. CUMJ 2021; 46: 381-6.
4. Gürbüz T, Dokuzeylül Gungor N. Hiperemezis gravidarum etiyopatogenezinde vitamin D eksikliğinin rolü var mı? Adıyaman Üni.Sağlık Bilimleri Derg 2018; 4: 761-71.
5. Dokuzeylul Gungor N, Gurbuz T,Ture T. Prolonged luteal phase support with progesterone may increase papules and plaques of pregnancy frequency in pregnancies through in vitro fertilization. An Bras Dermatol 2021; 96: 171-5.
6. Floreani, A. and M.T. Gervasi, New insights on intrahepatic cholestasis of pregnancy. Clin Liver Dis 2016; 20: 177-89.
7. Reyes H. Intrahepatic cholestasis. A puzzling disorder of pregnancy. J Gastroenterol Hepatol 1997; 12: 211-6.
8. Tran TT, Ahn J, Reau NS. ACG Clinical Guideline: Liver Disease and Pregnancy. Am J Gastroenterol 2016; 111: 176-94.
9. Reyes H. What have we learned about intrahepatic cholestasis of pregnancy? Hepatology 2016; 63: 4-8.
10. Diken Z, Usta IM, Nassar AH. A clinical approach to intrahepatic cholestasis of pregnancy. Am J Perinatol 2014; 31: 1-8.
11. Mutlu MF, Aslan K, Guler I, et al. Two cases of first onset intrahepatic cholestasis of pregnancy associated with moderate ovarian hyperstimulation syndrome after IVF treatment and review of the literature. J Obstet Gynaecol 2017 37: 547-9.
12. Batsry L, Zloto K, Kalter A, Baum M, Mazaki-Tovi S, Yinon Y. Perinatal outcomes of intrahepatic cholestasis of pregnancy in twin versus singleton pregnancies: is plurality associated with adverse outcomes? Arch Gynecol Obstet 2019; 300: 881-7.
13. Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet 2019; 393: 899-909.
14. Goulis DG, Walker IA, de Swiet M, Redman CW, Williamson C. Preeclampsia with abnormal liver function tests is associated with cholestasis in a subgroup of cases. Hypertens Pregnancy 2004; 23: 19-27.
15. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007; 39:175-91.
16. Alemdaroğlu S, Yılmaz Baran Ş, Durdağ GD, et al. Intrahepatic cholestasis of pregnancy: are in vitro fertilization pregnancies at risk? J Matern Fetal Neonatal Med 2021; 34: 2548-53.
17. Liu C, Gao J, Liu J, Wang X, et al. Intrahepatic cholestasis of pregnancy is associated with an increased risk of gestational diabetes and preeclampsia. Ann Transl Med 2020; 8: 1574.
18. Bolukbas FF, Bolukbas C, Balaban HY, et al. Intrahepatic cholestasis of pregnancy: spontaneous vs in vitro fertilization. Euroasian J Hepatogastroenterol 2017; 7: 126-9.
19. Shan D, Hu Y, Qiu P, et al. Intrahepatic Cholestasis of pregnancy in women with twin pregnancy. Twin Res Hum Genet 2016; 19: 697-707.
20. Feng C, Li WJ, He RH, Sun XW, Wang G, Wang LQ. Impacts of different methods of conception on the perinatal outcome of intrahepatic cholestasis of pregnancy in twin pregnancies. Sci Rep 2018; 8: 3985.
21. Çelik S, Çalışkan C. The impact of assisted reproductive technology in twin pregnancies complicated by intrahepatic cholestasis of pregnancy: a retrospective cohort study. Z Geburtshilfe Neonatol 2021; 225: 34-8.
22. Dokuzeylul Gungor N, Gurbuz T, Yurci A, Demircivi Bor E. Retrospective analysis of spontaneous pregnancy cases after in vitro fertilization six years of experience. JRM 2021; 66: 337-41.
23. Li L, Chen YH, Yang YY, Cong L. Effect of intrahepatic cholestasis of pregnancy on neonatal birth weight: a meta-analysis. J Clin Res Pediatr Endocrinol 2018; 10: 38-43.